IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Kreutzer *et al.*	Art Unit	: 1635
Serial No.	: 10/612,179	Examiner	: Tracy Ann Vivlemore
Filed	: July 2, 2003	Conf. No.	: 5239
Title	: METHOD AND MEDICAMENT FOR INHIBITING THE EXPRESSION OF A GIVEN GENE		

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REPLY TO FINAL OFFICE ACTION OF AUGUST 07, 2006

This is in response to the Final Office Action mailed August 7, 2006, with regards to the above referenced application. Claims 4-9 are pending.

Applicants respectfully request that the Examiner consider references numbered 134-154 on the information disclosure statement submitted January 8, 2004, and return an initialed copy of the corresponding page of the form 1449.

Rejections Under 35 USC 102

At page 2 of the Final Office Action, the Examiner has maintained the rejection of claims 4 and 6-9 as being anticipated by Crooke.

Applicants respectfully traverse this rejection based on the following remarks.

Crooke was investigating a putative dsRNAase in cells using what was called an "artificial substrate" (Table 1) that would mimic the association of a single strand RNA with an RNA target. To this end, Crooke synthesized dsRNA that would mimic the binding of a single stranded RNA cleavage agent with a target RNA sequence and then looked at the resultant product after incubation with various RNAases. The Examiner contends that these synthetic substrates meet all the limitations of the claims and would be expected to function as required by the claims.

Applicants respectfully assert that this is not the case and one would not expect that the synthetic substrates provided in Crooke would function in an RNAi process. Specifically, as will be outlined below, the RNAi process can tolerate some modifications to the dsRNA but

significant modification can either be toxic to a cell or lead to inactive molecules. The Prakash reference cited by the Examiner clearly demonstrates that dsRNAs that have an antisense strand that has a 2'MOE modification at the 5' and 3' end would not be active in the RNAi process. As such, the 4 dsRNAs disclosed in Crooke, which all contain at least an antisense strand having 4 (Ha-ras targeted) or 6 (C-raf target) 2'MOE at both of the 5' and 3' ends and near complete PS linkages in both the antisense and sense strands would be predicted as not meeting the limitation of the claims of "specifically inhibits the expression of said mammalian target gene" since they would be predicted to be inactive.

a) dsRNAs of Crooke. In Table 1, 4 highly modified dsRNAs are disclosed and are described at column 50, lines 51-60:

"The 'sense' strand was an oligoribonucleotide having phosphodiester linkages in an eight-base gap with flanks having either (a) residues with phosphorothioate linkages or (b) 2'-methoxynucleosides with phosphorothioate linkages. The 'antisense' strand in both substrates contained 2'-methoxy phosphorothioate wings on either side of an eight-base ribonucleotide gap having either phosphodiester or phosphorothioate linkages."

In summary, the 17mer dsRNA of Crooke that have sequence complementarity to Ha-ras would therefore have an antisense with 5' and 3' ends with a total of 9 2'MOE bases split between the ends and will additionally have either 9 or 16 PS linkages, paired with a sense strand that has 9 PS linkages. The 20mer dsRNA have sequence complementarity to C-raf would have an antisense with 5' and 3' ends with a total of 12 2'MOE bases split between the ends and would additionally have either 12 or 19 PS linkages, paired with a sense strand that has 12 PS linkages.

b) Prakash, cited by the Examiner, synthesized various dsRNAs containing three 2'MOE modifications at various positions within an antisense and sense strand siRNAs. at page 4250, column 2, Prakash states that "The potency of the 2'-OME modified siRNA duplexes was relatively limited compared to the unmodified siRNA 1:2 (Figure 6). This modification was not tolerated either at the 5' end (25:2 Figure 6) or at the 3' end (31:2 Figure 6) of the antisense strand."

From this passage as well and the next two paragraphs, it is clear the one would not expect the dsRNAs of Crooke to be functional siRNA molecules since they contain even more 2'MOE modifications on both the 5' and 3' end of the antisense strands than what Prakash shows to be nearly inactive (containing only 3 2'-MOEs on either the 5' or 3' ends).

Since there is significant teaching in the art as evidenced by Prakash cited by the Examiner that the agents of Crooke would not function as required by the claims, this rejection may be withdrawn.

At page 4 of the Office Action, The Examiner has maintained the rejection of claims 4-6 and 8 under 35 USC 102(e) as being anticipated by Fire as evidenced by Zhang. The Examiner has raised this as an inherency rejection holding that "the double stranded RNAs of Fire et al. while longer than 21 base pairs, are not products of nature and thus would be recognized as "isolated" dsRNAs. After cleavage by Dicer, the resulting short RNAs would also be isolated dsRNAs regardless of where the cleavage by Dicer occurs and Fire et al. as evidenced by Zhang provides inherent anticipation of the instant claims."

Applicants respectfully traverse this rejection based on the following remarks.

Applicants agree that the term "isolated" requires the hand of man and this is what distinguishes the present invention from that of Fire.

The Examiner is also correct in asserting that Fire teaches isolated dsRNA "longer than 21 base pairs" (greater than 25 is what is required by Fire).

However, when the >25 base pair dsRNAs of Fire are introduced into a cell where Dicer is present, although they are cleaved into dsRNAs 19-21 base pairs in length as taught by Zhang, these are no longer isolated, they are in the presence of cellular constituents that occur within a cell. Such dsRNAs are now a product of nature, though introduced as an isolated agent, Dicer (within the cell) then acts on it to produce a product of nature which is not longer in isolated form. Nowhere is there a disclosure in Fire to "isolate" a product produced within a cell after a long dsRNA is introduced within it.

The difference between an isolated 15-21 base pair dsRNA as claimed and a product that is produced within a cell by the inherent action of Dicer on a longer dsRNA substrate is significant. First, the product of the present invention would not be contaminated by cellular constituents present in the processed dsRNA of Fire. Second, the product produced within a cell from the action of Dicer on a longer dsRNA will be a variety of molecules with slightly different sequence compositions: a 25mer can be cleaved into 5 different 21mers and all of these will still not be in isolated form since they will be within a cell and be produced as a result of an act of nature.

As such, nowhere within Fire is there a teaching or a statement that can be read as teaching an "isolated" dsRNA of 15-21 base pairs as claimed or something that would inherently produce such an isolated molecule. If Fire teaches any isolated dsRNA, it is clearly longer than the claimed range, and any action of DICER that occurs in Fire happens within a cell and the resulting molecules are non-isolated molecules.

SUMMARY

Applicants have provided arguments to address each of the outstanding rejections of the claims. It is believed that the rejections have been addressed and that the application is in condition for allowance. It is requested that the Examiner contact Applicants undersigned representative if the Examiner believes that a telephonic interview would expedite this case.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States.

No fee is believed due. Please apply any necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 14174-105US5.

Respectfully submitted,

Date: November 6, 2006

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